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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,999	10/28/2003	Ilia Davydov	2528-10	4116
23117	7590	02/24/2006	EXAMINER	
NIXON & VANDERHYE, PC 901 NORTH GLEBE ROAD, 11TH FLOOR ARLINGTON, VA 22203			DESAI, ANAND U	
			ART UNIT	PAPER NUMBER
			1653	
DATE MAILED: 02/24/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	10/693,999		DAVYDOV ET AL.	
	Examiner		Art Unit	
	Anand U. Desai, Ph.D.		1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 3-8, 10, 12, 15-17, 35-47, 55 and 57-63 is/are pending in the application.
- 4a) Of the above claim(s) 5-8, 10, 12, 15, 16, 35-47 and 55 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 3, 4, 17 and 57-63 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>20050623</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This office action is in response to Amendment filed on November 17, 2005. Claims 5-8, 10, 12, 15, 16, 35-47, and 55 have been previously withdrawn. Claims 3, 4, 17, and 57-63 are currently pending and are under examination.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on June 23, 2005 is being considered by the examiner.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawal of Rejections

4. The rejection of claims 3, 4 and 17 under 35 U.S.C. 102(b) as being anticipated by Kleinschmidt et al. (Nucleic Acid Research 9(11): 2423-2431 (1981)) is withdrawn.

5. The rejection of claims 57, 58, 59, 62, and 63 under 35 U.S.C. 102(b) as being anticipated by Maeda, I. et al. (FEBS Letters 494: 181-185 (2001)) is withdrawn.

6. The rejection of claims 57-59, 62, and 63 under 35 U.S.C. 102(b) as being anticipated by Elsasser, S. et al. (Molecular Biology of the Cell 10: 3263-3277 (1999)) is withdrawn.

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New Rejection

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 3, 4, 17, and 57-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The added material which is not supported by the original disclosure are the allelic variants of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, and HSPC144. The section of the specification cited for support describes the general description of allelic variants, but does not recite allelic variants of the particularly claimed proteins. Applicant is required to cancel the new matter in the reply to this Office Action.

Maintenance of Rejections

Claim Rejections - 35 USC § 112

9. Claims 3, 4, 17, and 57-63 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
10. The claims are directed to a polypeptide having sequence "similarity". It is not clear what is encompassed by the word, "similarity?" Suggest sequence identity.

Response to Remarks

11. Applicants state “sequence similarity” is a well-defined phrase in the art of sequence analysis. Applicants describe a type of similarity based on electron distribution. Applicant's arguments filed November 17, 2005 have been fully considered but they are not persuasive. The word, “similarity” can have multiple interpretations, and it is not clear which particular interpretation should be used. For example, the amino acid sequence similarity could be based on molecular size. While the word, “identity” is clear to one ordinary skill in the art, as disclosed by Applicants response that describes an exact match between sequences.

12. Claims 3, 4, 17, and 57-63 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for an isolated complex comprising at least one ubiquitin and a protein selected from the group consisting of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, HSPC144, tau, Cullin 3, and CDC6, formed via the N-end rule mechanism, does not reasonably provide enablement for isolated complexes comprising **derivatives of ubiquitin** with **fragments and derivatives of proteins** selected from the group consisting of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, HSPC144, tau, Cullin 3, and CDC6, formed via the N-end rule mechanism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

13. The rejection is discussed in the office action mailed June 20, 2005.

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Response to Remarks

14. Applicants state a person skilled in the art would be able to practice the subject invention without undue experimentation in view of the disclosure in the specification and further in view of the high level of skill in the relevant art. Applicants state a skilled artisan regularly engages in such experimentation. Applicants cite examples 2-6, and corresponding gel electrophoresis images in figures 3-7 to describe N-end rule ubiquitination of protein fragments.

Applicant's arguments filed November 17, 2005 have been fully considered but they are not persuasive. The claims as amended are drawn to an isolated complex comprising at least one ubiquitin or derivative thereof, and a protein, wherein the protein can include allelic variants, fragments, and derivatives of a group of proteins. There is unpredictability in the art with regard to the tertiary structure required for the interaction of substrate with the cognate E3 ubiquitin-protein ligase enzymes. Experiments have shown that optimal binding of substrate with E3 ubiquitin ligase may require a specific conformation. There is also a limited understanding of particular E3 ubiquitin ligase active sites that are required during enzyme-substrate interaction (see page 4 of office action mailed June 20, 2005, paragraphs 3 and 6 of the Wands analysis for cited reference). Therefore, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8USPQ2d at 1404 (*Fed. Cir.* 1988). Thus, absent direction regarding whether the structure of the polypeptides can tolerate the modifications contemplated, one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims.

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15. Claims 3, 4, 17, and 57-63 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

16. The rejection is discussed in the office action mailed June 20, 2005.

Response to Remarks

17. Applicants state the pending claims are clear in view of the disclosure in the specification and further in view of what is known in the art. Applicants cite page 43-45 to describe examples of protein variants that are encompassed by the claimed invention.

Applicant's arguments filed November 17, 2005 have been fully considered but they are not persuasive. The claims as amended are drawn to an isolated complex comprising at least one ubiquitin or derivative thereof, and a protein, wherein the protein can include allelic variants, fragments, and derivatives of a group of proteins. The specification does not clearly describe the derivatives of ubiquitin, or allelic variants, fragments, and derivatives of the group of proteins currently claimed. Which 50 amino acids having at least 90% sequence similarity to sequences within their corresponding proteins are capable of forming a conjugate through an N-end rule ubiquitination process? When describing the fragments and derivatives of the corresponding proteins, do the 50 amino acids have to be 50 consecutive amino acids or any 50 amino acids? Further, what similarity is applied, if as Applicants state on page 11 of the remarks that a variant

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can be one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue?

Claim Rejections - 35 USC § 102

18. Claims 57, 58, 59, 62, and 63 stand rejected under 35 U.S.C. 102(b) as being anticipated by Morishima-Kawashima, M. et al. (Neuron 10(6): 1151-1160 (1993)).

19. The rejection is discussed in the office action mailed June 20, 2005.

Response to Remarks

Applicants state that out of six ubiquitinated sequences four start with glutamic acid, one starts with valine, and one starts with serine – none of which is a destabilizing N-terminal residue required for N-end rule ubiquitination. Applicant's arguments filed November 17, 2005 have been fully considered but they are not persuasive. Morishima-Kawashima, M. et al. does disclose the ubiquitination of tau protein from purified fractions of Alzheimer's disease brain tissue (mammalian cells; see office action mailed June 20, 2005). Varhavsky (IDS document TR, filed Feb. 16, 2005) does disclose destabilizing amino acids including glutamic acid (E), and serine (S) in mammalian cells (see Figure 1, page 12143). Therefore, the ubiquitination reaction does occur in mammalian cells using glutamic acid and serine amino acid residues in the N-end rule pathway.

Conclusion

20. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

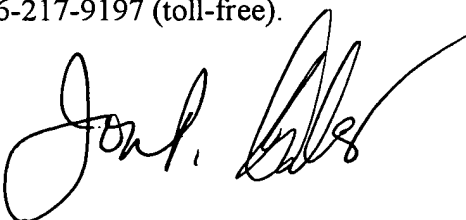
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 15, 2006



JON WEBER
SUPERVISORY PATENT EXAMINER